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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,877	02/02/2005	Takehiko Nomura	0020-5340PUS1	5247

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EXAMINER	
MACAULEY, SHERIDAN R	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
05/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,877	NOMURA ET AL.	
	Examiner	Art Unit	
	Sheridan R. MacAuley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,11,14,18 and 41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,11,14,18 and 41-47* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment and supplemental amendment were received and entered on December 10, 2007 and January 9, 2008, respectively. All evidence and arguments have been fully considered. Claims 1-5, 7-10, 12-13, 15-17 and 19-40 are cancelled. New claims 42-47 have been added. Claims 6, 11, 14, 18 and 41-47 are pending.

Specification

1. Objections to the specification have been withdrawn due to amendment.

Claim Objections

2. Claim 11 is objected to because of the following informalities. It is recommended that the claim be amended as follows: The term "claim 6,which" should be amended to read "claim 6, which". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Rejections under 35 USC 112 have been withdrawn due to amendment.

5. Claim 6 is rendered indefinite by the recitation of "25 degrees C." in the fourth line of the claim. Claim(s) must be in one sentence form only (see MPEP 706.03(d)).

Claim Rejections - 35 USC § 102

6. Rejections under 35 USC 102 have been withdrawn due to amendment.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 6, 11, 14, 18 and 41-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Azuma (EP 1097715 A1, cited in prior action) in view of Van Nest et al. (EP 0399843 A2). Claim 6 recites a paste comprising Bacillus Calmette-Guerin – cell wall Skeleton (BCG-CWS), wherein the paste comprises 6.6 g to 35.2 g of squalane per about 0.67 g of BCG-CWS and has the following properties: (1) a viscosity between 0.2 and 0.7 poise at 25 degrees C and (2) comprising an assembly of BCG-CWS particles, wherein the particle diameter is from 0.1 microns to 20 microns in the particle size distribution and showing a single peak distribution with D10%: 0.23 ± 0.05 microns and D90%: 0.60 ± 0.05 microns. Claim 11 recites the paste of claim 6, which is obtained by a process for preparation which comprises the following steps: (1) mixing the BCG-CWS and squalane in an organic solvent used as a dispersion-aiding solvent, wherein the organic solvent is hexane or heptane which comprises 5 to 20 (v/v) aiding solvent, wherein the organic solvent is hexane or heptane which comprises 5 to 20 (v/v) of ethanol; and (2) a step of removing the organic solvent in (1) by distillation. Claim 14 recites the paste according to claim 1 that is formulated as an oil-in-water emulsion, which comprises 0.66 g of the BCG-CWS, 0.4 wt% to 8 wt% of the squalane, 0.01 to 3% of polyethyleneoxysorbitan fatty acid ester and 1 to 10% of mannitol per 2L of water. Claim 18 recites the paste according to claim 17, wherein the polyethyleneoxysorbitan fatty acid ester is TWEEN 80 (polysorbate 80). Claims 41 and 42 recite a pharmaceutical composition comprising the emulsion according to claim 14, or claim 6 or 11, respectively. Claims 43 and 44 recite the paste of claim 6 wherein the paste has a viscosity of between 0.43 and 0.55 poise, specifically 0.43, at 25 degrees C. Claim 45

recites the paste according to claim 6 where the paste comprises 8.9 to 17.9 g of squalane per about 0.67 g of BCG-CWS. Claim 46 recites a paste comprising BCG-CWS and squalane, wherein the weight squalane : weight BCG CWS of said paste is 9.8 to 52.5, and wherein the viscosity of said paste is between 0.2 and 0.7 poise at 25 degrees C. Claim 47 recites the paste of claim 46, formulated as an assembly of BCG-CWS particles, wherein the particles have a diameter of between 0.1 microns to 20 microns and has a single peak of particle size distribution with D10%: 0.23 ± 0.05 microns and D90%: 0.60 ± 0.05 microns

11. Azuma teaches a paste comprising bacterial CWS (including BCG-CWS, i.e. CWS from the BCG strain of *Mycobacterium bovis*) and an oil (squalane). Although Azuma does not disclose the viscosity of the paste, it is made by nearly identical methods to those described in the instant application (p. 17, line 57-p. 18, line 5). The paste of Azuma would therefore inherently have a viscosity within the disclosed range. Azuma teaches that the particle diameter of the droplets is from 0.1 to 20 microns (p. 3, lines 10-18, p. 4, lines 6-14 and p. 6, lines 13-17). Azuma teaches that the paste is formulated as an assembly of bacterial CWS particles, and that the paste is formulated as an oil-in-water emulsion (p. 4, lines 4-22). Azuma et al. teaches that the emulsion can be used as a pharmaceutical composition (p. 8, lines 51-53). Azuma teaches that the composition may comprise 0.2% TWEEN 80 (i.e., polysorbate 80), 2.3% mannitol, about 1.6 weight% of oil and water (p. 10, lines 1-8, table 1). Azuma teaches that the compositions may comprise between about 1 g of bacterial CWS per 2 liters of water (p. 10, lines 1-8). Azuma also teaches that a composition with a single peak for particle

size is preferable because it is indicative of stability of the composition (p. 6, lines 18-23).

12. Azuma does not specifically teach a composition comprising all of the claimed rations of BCG-CWS to squalane, or a composition wherein the particle size distribution shows a single peak as well as D10%: 0.23 ± 0.05 microns and D90%: 0.60 ± 0.05 microns.

13. Van Nest teaches a composition which is an oil-in-water emulsion comprising a muramyl dipeptide derivative (MTP-PE, see p. 2, lines 41-55) and an oil, wherein the particle size is less than one micron, specifically between 0.5 and 0.8 microns (p. 24, lines 25-42). Van Nest teaches that reducing oil droplet size improves the adjuvant performance (p. 24, lines 41-42). Van Nest teaches a method of reducing oil droplet size in the composition (p. 7, lines 12-22).

14. At the time of the invention, a composition comprising nearly all of the claimed elements was known, as taught by Azuma. Although Azuma does not disclose the viscosity of the paste, it is made by nearly identical methods to those described in the instant application (p. 17, line 57-p. 18, line 5). The paste of Azuma would therefore be expected to have a viscosity within the disclosed range. It was also known at the time of the invention that the particle size of oil-in-water compositions comprising similar components could be reduced within the claimed range, and that compositions comprising a single peak for particle size distribution are preferential, as taught by Van Nest and Azuma, respectively. One of ordinary skill in the art would have been motivated to reduce the particle size of the oil-in-water emulsion of Azuma to the range

taught by Van Nest because Van Nest teaches that the reduced droplet size improves the performance of the compound as an adjuvant. Furthermore, Azuma teaches that the amount of squalane in the compositions may be varied to produce the desired effect (p. 5, par. 20); one of ordinary skill in the art would therefore have been motivated to modify the ratio of BCG-CWS to squalane in the course of routine experimentation, and could have done so with a reasonable expectation of success. One would have a reasonable expectation of success in reducing droplet size because methods to reduce droplet size were successfully employed by Van Nest using a similar composition. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

15. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

16. Applicant's arguments filed December 10, 2007 and January 9, 2008 have been fully considered but they are not persuasive. Applicant argues that one of ordinary skill would not have a reasonable expectation of success in combining the teachings of Azuma and Van Nest to arrive at the claimed invention because Van Nest teaches the preparation of a different composition than the instantly claimed composition. This is not found persuasive, because the Azuma and Van Nest references are both directed to the production of oil in water emulsions comprising bacterial cell walls (see Azuma, abstract, and Van Nest, p. 7, lines 38-47). Although applicant argues that Van Nest's

compositions differ from those recited by the claims because applicant's compositions comprise more cell wall components than those of Van Nest, this is not found to be persuasive because Van Nest teaches the preparation of compositions comprising killed bacterial cells (p. 7, lines 44-45), which comprise all cell wall components. One of ordinary skill in the art would therefore have recognized that the teachings of Van Nest would have been applicable to the modification of the oil in water emulsions of Azuma, and would have had a reasonable expectation of success in applying the techniques of Van Nest to the compositions of Azuma.

17. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). One of ordinary skill in the art would have recognized the desirability to modify the teachings of Azuma with those of Van Nest because Van Nest teaches that decreasing droplet size increases adjuvant performance of the emulsion (p. 24, lines 40-42). Since Van Nest teaches the desirability for decreasing droplet size of such compositions, one of ordinary skill in the art would have been motivated to decrease the droplet size of the composition of Azuma.

18. Therefore, applicant's arguments have been fully considered, but they have not been found to be persuasive.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan R. MacAuley whose telephone number is (571)270-3056. The examiner can normally be reached on Mon-Thurs, 7:30AM-5:00PM EST, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SRM

/Ruth A. Davis/
Primary Examiner, Art Unit 1651